ADULT NEUROGENESIS IN THE DENTATE GYRUS

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INTRODUCTION

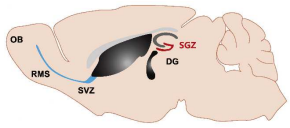
- During several years, adult neurogenesis was not accepted by the scientific community. It was not until the end of the twentieth century when it became a fact.
- At the beginning, neurogenesis was considered more of a vestigial process than an important one. However, its different functions and pathological implications made them an important mechanism of the brain.
- Lots of brain regions are suspected of being potential neurogenic sites, but only neurogenesis in the hippocampus and the olfactory bulb have been fully proved.

METHODS

- Search on the internet through "Pubmed" database with "adult neurogenesis [AND] dentate gyrus" as key words.
- Due to the broad quantity of information with this simple inquiry, search criteria was adapted to articles only from 2005 and review format.
- Finally, there were chosen 20 relevant reviews from which we obtained other original articles for the understanding of the field.

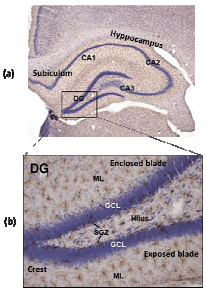
BASES OF NEUROGENESIS

- Neurogenesis in mammals has been only proven in two restricted areas of the brain: the subventricular zone of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG)(Figure 1).
- New-born cells originate from adult neural stem cells (NSCs), which are located together with endothelial cells, astrocytes and oligodendrocytes in a structure called neurogenic niche.
- After birth, they migrate into the correct location the granule cell layer (GCL) in the case of SGZ.



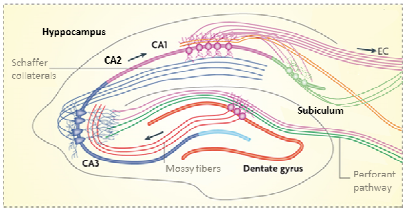
▲ **Figure 1. Schematic image of the adult neurogenic zones**. OB, olfactory bulb, RMS, rostral migratory stream; SVZ, subventricular zone; DG, dentate gyrus; SGZ, subgranular zone.

WHERE? HIPPOCAMPAL FORMATION



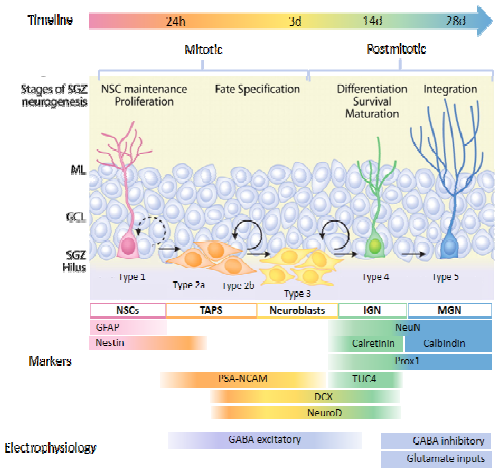
▲ **Figure 2. Section of the brain immunolabeled with Nissl staining**. (a) general vision of the hippocampal formation. (b) focus on the dentate gyrus. DG, dentate gyrus; ML, molecular layer; GCL, granule cell layer; SGZ, subgranular zone.

- DG is located within the hippocampal formation, a structure comprised of different sections (Figure 2a).
- DG is not uniform and have also diverse layers (Figure 2b).
- The hippocampal formation comprises a complex network of intern connections, essential for its proper functioning (Figure 3)



▲ **Figure 3. Intern connections within the hippocampal formation.** The initial fibers come from the enthorrinal cortex (EC), and them subsequent axons projects come following the dentate gyrus, the CA3, the CA3 and then EC or the subiculum.

FASES OF NEUROGENESIS IN THE DENTATE GYRUS



▲ **Figure 4. Different stages of neurogenesis.** (migration is not represented). ML, molecular layer; GCL, granule cell layer; SGZ, subgranular zone; NSC, neural stem cell; TAPS, transiently amplifying cells; IGN, inmature granule cell; MGN, mature granule cell; DCX, doublecortin; PSA-NCAM, polysialated form of neural cell adhesion molecule; CRMP4, collapsin response mediator protein 4; GFAP, glial fibrillary acidic protein.

Adult neurogenesis is a gradual and multistep process with different stages which implies the expression of diverse molecular makers (Figure 4). In general neurogenesis goes through the maintenance and proliferation of NSCs, which subsequently lead to a fate specification step where types 2 and 3 are comprised. After the mitotic section, type 4 neurons have to differentiate, survive, and mature in order to become granule neurons. Finally, type 5 neurons integrate gradually in the existing system.

MIGRATION

- Tangential migration of neuroblasts and postmitotic cells. At the same time, they leave a trailing process in the hilus that will become the axon.
- Radial migration to the GCL of neuroblasts and postmitotic cells, while their dendrites grow.

INTRINSIC AND EXTRINSIC REGULATING FACTORS

INTRINSIC MECHANISMS THAT REGULATE NEUROGENESIS

Regulatory factor	Effect on neurogenesis	General information
Morphogens		
Wnt	Increase proliferation, differentiation and cell survival	Induces synthesis of NeuroD and increase the expression of LINE-1
Shh	Increase NSCs maintenance and proliferation	
Transcriptional factors		
Sox	Increase maintenance and proliferation	Acts through different subtypes, specially Sox2
NeuroD1	Increase differentiation	Basic helix-loop-helix transcriptional factor
Prox1	Increase survival and maturation	Mainly regulated by Wnt signals

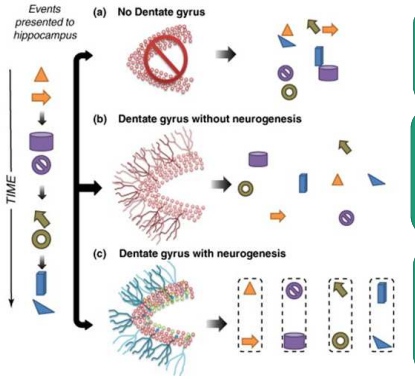
EXTRINSIC MECHANISMS THAT REGULATE NEUROGENESIS

Regulatory factor	Effect on neurogenesis	General information
Neurotransmitters		
Glutamate	Decrease and increase in proliferation	Decrease acting through NMDA receptors and increase through AMPA receptors
GABA	Increase differentiation	
Growth factors		
VEGF	Increase proliferation	Link between neurogenesis and angiogenesis
Hormones		
Glucocorticoids	Decrease proliferation	Relationship with the decrease neurogenesis in stress pathology.
Environmental/ physiological influences		
Voluntary physical activity	Increase proliferation	Effects through increases mainly in VEGF and other growth factors
Learning	Increase survival rate	Only when those tasks involve the hippocampus

▲ **Tables 1 and 2.** VEGF, vascular endothelial growth factor; GABA, gamma-aminoglutidic acid; Shh, sonic hedgehog; Prox1, prospero homeobox protein 1; Sox, Sry-related HMG box; NMDA, N-methyl-D- aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.

FUNCTIONAL IMPLICACIONS OF ADULT NEUROGENESIS

- DG is well-known for its implication in pattern separation of memories.
- Young neurons display a set of characteristics a little bit different than their older companions. Mainly because of that, they have a role in pattern integration (Figure 5).
- However, as they mature, they become undistinguishable from the previously integrated neurons. Consequently, they have a normal role in pattern separation (Figure 6).



- Events are not separated.
- Impaired discrimination of similar events.

- Events are highly separated.
- Discrimination is possible.
- Temporal relationships are not encoded.

- Events are highly separated.
- Discrimination is possible.
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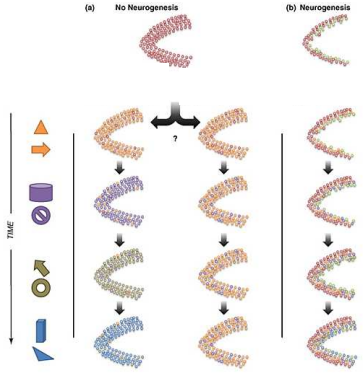
▲ **Figure 5. How DG and new neurons might affect pattern separation**. Each panel represents how a series of temporally discrete events.

- Incorporation of new information that overwrites old information.
- New memories are encoded by the remain "free" neurons.

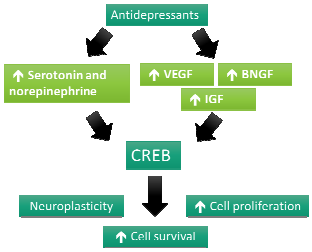
New information is encoded by new neurons and so old information remains intact.



▲ **Figure 6. Alternative theories of neurogenesis depletion on the DG long term.** Each column represents how the DG would acquire information about events presented over extended time scales.

PATHOPHYSIOLOGY: DEPRESSION

- There are lots of illnesses where neurogenesis is affected. The most studied one is depression.
- Different environmental conditions and antidepressants that confer antidepressesant-like responses are associated with an increase in neurogenesis.
- The precise mechanisms are still a mystery. However, some possible actions of antidepressants include the increasing of diverse components well-known for enhancing neurogenesis. (Figure 7).



▲ **Figure 7.** Antidepressants can, on one hand, increase the amounts of serotonin and norepinephrine and, on the other hand, stimulate de secretion of grow factors such as VEGF. Both mechanisms stimulate de signaling cascade of cAMP response element binding (CREB) protein, which utterly results in an increase of cell survival and proliferation that leads to neuroplasticity.

CONCLUSION

- Surprisingly, with this process we are not only able of generating new neurons but also of integrating them physically and functionally in a complex and crowded system.
- Each day, new illnesses seem to be related in some way to neurogenesis, emphasizing even more the functional role of this process.
- We still lack information about the complete function of these new-born cells and so tenacious efforts will be needed in order to understand completely this mechanism and use this knowledge for new therapeutic approximations.

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